Commentaries on Viewpoint: Can elite athletes benefit from dietary nitrate supplementation?

LACK OF EFFECT OF DIETARY NITRATE IN ELITE ATHLETES MAY BE DUE TO DILATION OF NON-PRIORITIZED VASCULAR BEDS

TO THE EDITOR: As Jonvik and colleagues (3) describe, dietary nitrate appears to improve the performance of well-trained athletes, whereas all studies in professional elite athletes have shown no effect or even a detrimental effect. One explanation they do not touch upon is the fact that nitrate-derived nitric oxide production is not site specific and thus causes vasodilation of other vascular beds, which could impair blood flow to prioritized muscles during maximal exertion. In maximal, whole body exercise there is evidence that blood flow can be reduced to other muscle groups to maintain total conductance within the limit of maximal cardiac output (2). Elite athletes are probably more prone to working close to this limit. In addition, nitric oxide production from nitrate seems to be enhanced by hypoxia (4), and non-prioritized muscles and other organs would tend to be more hypoxic during maximal exertion. Nitrate-derived nitric oxide could thereby target these vascular beds specifically, which is supported by recent data showing that nitrate supplementation impairs the generalized vasoconstriction of the diving reflex (5) and has no effect during high-altitude running (1). Thus nitrate-mediated vasodilation could reduce oxygen delivery to critical muscles in elite athletes working very close to their maximal cardiac output by dilating non-prioritized vascular beds.

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Michael Hultström
Department of Medical Cell Biology and Department of Surgical Sciences
Uppsala University

THE MINIMUM BENEFIT OF DIETARY NITRATE SUPPLEMENTATION IN ELITE VS. RECREATIONAL ATHLETES: A TOPIC OF DEBATE?

TO THE EDITOR: The article by Jonvik and colleagues (1) raises the question of whether elite athletes are benefited by ergogenic properties of nitrate supplementation compared with recreational athletes. In the conclusion, authors state that “recent data tend to suggest that the ergogenic properties of nitrate supplementation are restricted to the recreational athlete and not evident in highly trained, elite athlete.” Nitric oxide (NO) production increases in response to physical activity, a requirement to maintain homeostasis during exercise (4). Therefore, ergogenic supplements that favors NO formation and cell metabolism (2) will certainly favor endurance in individuals whose NO bioavailability is lower. Notoriously (but not necessarily restrict to), recreational athletes as well as sedentary individuals will have a greater benefit of nitrate supplementation. Besides, the comparison between kayakers, cross-country skiers, cyclists, and 1,500-m runners is absolutely complex. The mechanical demands for these different modalities are totally different and the synergistic actions between NO and other vasoactive factors, including endothelin, EDHF, prosta-cyclin, angiotensins, Bradykinin, and others must be taken in consideration for each region on demand. Even if we suppose that $V_{O2max}$ was compared and assumed to be equivalent between individuals of these different groups, the localized vascular reactivity differs for different modalities of exercise (3, 5) and the contribution of NO for each specific condition is unknown. In conclusion, to be considered a topic of debate, the question raised by Jonvik and colleagues requires extensive additional knowledge from integrative physiology and more homogeneous group approach.

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Cristiane Amorim de Paula
Marco Antônio Peliky Fontes
Department of Physiology & Biophysics
Federal University of Minas Gerais, Brazil

COMMENTARY ON “CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?”

TO THE EDITOR: Jonvik and colleagues (3) have raised a really interesting and burning question about the ergogenic benefits of nitrate supplementation in elite athletes. In our previous experiments (4) we have seen that the effects of nitrate supplementation on oxygen consumption and running performance are significantly related to the individual aerobic fitness level, with no benefits observed on highly trained subjects ($V_{O2max}$ >60 ml·kg$^{-1}$·min$^{-1}$). Thus our results seem to suggest that nitrate supplementation may be ineffective in elite athletes. However, “responders” are present among elite ath-
letes (1–2, 5) and the potential effects of nitrate supplementation on these subjects are unclear and need further examination. As indicated by a significant negative correlation between the increase of plasma nitrite after supplementation and performance in our results, the magnitude of the variance in nitrate/nitrite concentration after supplementation may be a crucial point. In accordance, a greater increase in nitrite levels after supplementation has been observed in “responders” (5). Thus, in our opinion, more attention should be paid to the effects of nitrate supplementation on nitrate/nitrite levels than on the aerobic fitness of the subject itself, although these two aspects are related. Future studies need to investigate in elite athletes the “dose-response” relationship between nitrate supplementation and the amount of change in blood concentration of nitrate/nitrite to clarify if elite athletes may request a higher dose of nitrate or a longer supplementation period to improve their performance.

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Simone Porcelli1
Giuseppe Bellistri1,2
Lorenzo Pugliese1
Letizia Rasica1
Mauro Marzorati1
Gaspare Pavei3
1Institute of Molecular Bioimaging & Physiology National Research Council, Italy
2Department of Biomedical Sciences for Health University of Milan, Italy
3Dept of Pathophysiology & Transplantation University of Milan, Italy

ELITE ATHLETES CAN BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION

TO THE EDITOR: The Viewpoint article published in the Journal of Applied Physiology by Jonvik et al. (3) raised pertinent questions regarding nitrate supplementation. A crucial consideration that was absent from that Viewpoint concerns the dependence of the degree of benefit(s) on the event and environment in which the athlete performs/competes. As highlighted by Jonvik et al. (3), there is considerable evidence to support beneficial impacts of nitrate supplementation on the physiological function of type II, but not type I, muscle fibers. Our laboratory has demonstrated that nitrate supplementation via beetroot juice preferentially elevates blood flow and the microvascular PO2 (pressure required for blood-myocyte O2 flux) within fast twitch muscles. This effect is likely dependent upon the lower PO2 environment within these tissues (4), which facilitates reduction of nitrite to nitric oxide. This effect may underlie the improved VO2 kinetics and tolerance to exercise evident during severe-intensity exercise transitions as well as the improved performance at simulated altitude observed in humans (1, 5). In this regard, athletes competing in events held at altitude, particularly those with frequent transitions in work rate, for example, runners of the Ultra-Trail Du Mont Blanc, a trail run of ~170 km with ~10,000 m of positive elevation change, or other elite mountain athletes (e.g., climbers or cyclists) may potentially see improvements in performance. Considering further the increase in contractile function of type II muscle reported by Hernandez et al. (2) after nitrate supplementation it seems logical that elite power athletes (power-lifters) may also potentially benefit from nitrate supplementation.

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Scott K. Ferguson
Clark T. Holdsworth
Timothy I. Musch
David C. Poole
Department of Anatomy and Physiology
Department of Kinesiology
Kansas State University

VIEWPOINT: BENEFITS FROM NITRATE SUPPLEMENTATION IN HYPOXIA?

TO THE EDITOR: Jonvik et al. (3) do not discuss potential benefits of nitrate supplementation in subjects exposed to hypoxia, when O2 supply limits O2 uptake and an O2 sparing effect of NO (4) could potentially improve performance. In hypoxia, increased NO levels are associated with decreased risk for altitude illness and potentially with increased performance (2, 4). Nitrate, by elevating NO bioavailability, might improve exercise performance in three ways: 1) hypoxic pulmonary vasoconstriction might be mitigated, improving right heart function and thereby exercise performance (5); 2) cerebral blood flow and cerebral tissue oxygenation might be improved, potentially increasing motor drive; and 3) by oxygen sparing, NO might allow more aerobic power for a given oxygen consumption (4). Arnold et al. (1) found that nitrate supplementation did not consistently enhance running performance of well-trained ath-

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letters in hypoxia during incremental (at 4,000 m) and 10-km time trial (at 2,500 m) exercises. They did not look at hypoxic pulmonary arterial vasoconstriction, and the acute hypoxic exposure they used may have preceded full hypoxic pulmonary artery vasoconstriction. Nevertheless, as discussed by Jonvik et al. (3), perhaps only less trained athletes positively respond to nitrate supplementation (1, 3). Future studies should focus on identifying the factors that could explain why some athletes are more responsive to nitrate supplementation than others. For athletes competing at altitude this should be done in hypoxia too. So far there is no evidence for systematic nitrate supplementation for prevention of hypoxia-induced pulmonary hypertension and for improving exercise performance in hypoxia in trained athletes.

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Nicolas Bourdillon

*ISSUL, Université de Lausanne*

NITRATE SUPPLEMENTATION: SOME ELITE ATHLETES MAY BENEFIT AND HARM IS UNLIKELY

TO THE EDITOR: The Viewpoint of Jonvik and colleagues (3) provides insight into why nitrate (NO₃⁻) supplementation may have fewer benefits for elite athletes and why studies in highly trained populations have reported mixed outcomes. Based on currently available literature, it is reasonable to conclude NO₃⁻ is more effective in improving performance in lower caliber or lesser-trained athletes. However, given that “responders” are still apparent in studies involving elite cohorts and few side effects other than pink urine/stools after beetroot juice ingestion have been reported, NO₃⁻ consumption may still be a useful nutritional strategy for high-caliber athletes.

The efficacy of NO₃⁻ supplementation is likely associated with the specific conditions of exercise. Shorter, high-intensity events may benefit more because of hypoxic and acidic stimulation of the NO₃⁻/NO₂⁻ reduction pathway and the relatively greater involvement of type II fiber (2). In particular, the exaggeration of these conditions in smaller muscle groups would appear to favor upper body-dominant exercise (2), possibly explaining observations of benefits to competitive athletes in kayaking and rowing (1, 4).

Another potential application of NO₃⁻ supplementation is to attenuate the ergolytic effects of hypoxia (5). This may be useful to athletes undertaking altitude training or competing in high-altitude environments (e.g., cross-country skiers, mountainous cycling stages) where O₂ availability is challenged. Research to verify this effect in elite subjects is required.

Therefore, although NO₃⁻ supplementation is more valuable to lesser trained or lower caliber athletes, there are perhaps certain sports, events, and conditions where it may assist elite competitors.

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Matthew W. Hoon

*School of Exercise Science*

*Australian Catholic University*

Louise M. Burke

*Sports Nutrition*

*Australian Institute of Sport*

Mary MacKillop Institute for Health Research

*Australian Catholic University*

COMMENT ON “CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?”

TO THE EDITOR: The authors (2) addressed an interesting question, “Can elite athletes benefit from dietary nitrate supplementation?” In their discussion, the authors point out that a positive response could make the difference that determines if a new world record is set. However, a negative response could also be helpful in guiding coaches and athletes in their training regimes. Legitimate questions deserve legitimate answers that can only be gained through carefully planned research.

All exercise training programs should be guided by scientific principles that include intensity, frequency, duration, and specificity of exercise. The authors mentioned but did not elaborate on the importance of the specificity of exercise testing. The effects of exercise training and/or a supplement on exercise performance can only be answered if the mode of exercise testing is the same as the training mode. The energy systems, muscle group recruitment, and the biomechanics vary according to the specific demands of the mode of exercise. Nitrate (NO₃⁻) supplementation has been used to enhance exercise performance with limited success in elite athletes (1, 3, 4, 5). When cross-country skiers were tested on a treadmill after nitrate supplementation, no significant differences were observed in running performance (3, 5). After NO₃⁻ supplementation, kayakers tested on a laboratory kayak ergometer or in the water, significant improvements in time trials were noted (4). However, NO₃⁻ ingestion did not affect power output in elite cyclists when tested in the same mode (1). Therefore, more research is needed that incorporates the specificity principle to resolve the question (2).
Can elite athletes benefit from dietary nitrate supplementation? Greater ergogenic opportunity in the master athlete?

To the Editor: Although nitrate supplementation has been generally proposed for enhancing aerobic performance, Jonvik et al. (4) underlined only briefly the putative role of nitric oxide (NO) bioavailability for improving contractile function especially in fast-twitch (FT) muscle fibers. Interestingly, blood flow, vascular conductance, and microvascular oxygen pressure were shown to be augmented mostly in FT after dietary nitrate supplementation (3). The latter may in turn support the benefit of nitrate supplementation found to improve repeated sprints performance in team-sport athletes (5). Moreover, when exercising at high intensity with an added hypoxic stimulus, a NO-mediated compensatory vasodilation prevails over the increased sympathetic vasoconstrictor activity directed toward skeletal muscle (occurring largely within FT as shown in rats) (1, 3). For instance, repeated sprints fatigue was delayed after specific repeated sprint training in hypoxia (RSH), soliciting mostly FT supposedly due to such a NO-mediated regulation (1). Taken together, these results suggest a potential benefit of nitrate supplementation to augment NO bioavailability and likely improve repeated sprints ability (RSA), of interest in team sports. With the difference in nitrosative stress reported between hypobaric and normobaric hypoxia (2), future studies should determine if nitrate supplementation enhances the efficiency of RSH for improving RSA and the influence of the type of hypoxic environment.

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Benjamin T. Corona
Extremity Trauma and Regenerative Medicine
United States Army Institute of Surgical Research
Fort Sam Houston, Texas

Michael S. Green
Department of Kinesiology & Health Promotion
Troy University
Troy, Alabama

COMMENTARIES ON VIEWPOINT: CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?

TO THE EDITOR: A recent Viewpoint (5) showed that nitrate supplementation for elite athletes promotes relevant performance benefits. Despite the significant results, these gains showed small effect size (3). It should be highlighted that in high-level competitions, the differences in the results between the first and third place is less than 0.5%. These differences, despite being small, may have great practical relevance (3, 5). However, it is necessary to analyze carefully the statistical procedures adopted in those studies to establish the relevance of small significant differences of nitrate supplementation for elite athletes because of the possibility of occurrences by chance. In this regard, all studies cited by Jonvik et al. (5) used small samples with statistical significance level set at $P < 0.05$. Nevertheless, for small samples, the number of pairs in a matched comparison is also small, affecting statistical power, because outliers carry more weight in analysis than if more data were available to buffer their effects (1). Additionally, statistical significance should be decreased to $P < 0.01$ to prevent type 1 error (2).

Furthermore, the positive effects from nitrate for elite athletes is often related to higher doses (8.4–16.8 mmol) with long-term supplementation (5–15 days) (5). However, higher nitrate doses may be toxic and result in intolerance and endothelial dysfunction (3). In addition, there is no evidence regarding the long-term supplementation with high nitrate doses on health risk for athletes (5). Thus the nitrate supplementation would not be a good strategy because the results are statistically weak and possibly offer health risk.

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Anderson Luiz B. da Silveira
Federal Rural University of Rio de Janeiro-UFRRJ
Brazil

COMMENTARY ON VIEWPOINT: CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?

TO THE EDITOR: Dietary nitrate supplementation promotes several physiological benefits in a variety of populations. In the recent Viewpoint, Jonvik et al. (2) question whether nitrate supplementation elicits exercise performance benefits in elite athletes. Although the majority of studies in elite athletes demonstrate that nitrate supplementation does not improve VO$_2$ kinetics or exercise performance, evidence suggests that there might be “responders” and “nonresponders” within highly trained individuals (1, 5). That is, despite lack of statistical significance for group means, certain elite athletes demonstrate improved exercise performance after nitrate supplementation. It has been postulated that the difference in responsiveness may be a function of training status (1) or due to higher baseline NO levels typically observed in elite athletes. However, we postulate here that it could be due to the large variability in nitrate reductase activity within the oral cavity to convert nitrate to the more bioactive molecule, nitrite (4). Differences in individual’s oral flora (microbiota) have a profound effect on plasma nitrite levels. Packer et al. (3) described individuals as being consistently high, medium, or low nitrate converters. Moreover, increased plasma nitrite after acute nitrate supplementation is what is related to the improvement in performance in some well-trained male cyclists (5). Such differences in the ability to reduce nitrate to nitrite could have important experimental consequences because nitrate, not nitrate, correlates to physiological improvements. To avoid the variability observed in nitrate reductase activity, nitrate supplementation studies should be conducted to elucidate the improvements on exercise performance in elite athletes.

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Amy L. Sindler
Department of Health & Human Physiology

Darren P. Casey
Department of Physical Therapy & Rehabilitation Science
University of Iowa

ELITE ATHLETES MAY BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION THROUGH REGULATION OF BODY TEMPERATURE

TO THE EDITOR: Parallel with debates, nitric oxide (NO) supplementation affects speed, strength, and endurance when con-
consumed by elite athletes (3), and there is evidence to suggest NO helps regulate body temperature in situations of internal or external thermal challenges (1, 2, 4). Theoretically, heat dissipation and body temperature regulation can be altered through vasodilation and CNS control (2, 4); furthermore, it has been demonstrated that NO plays a role in sweat regulation and is an effective central modulator of temperature regulation (2). The potential to make thermoregulation more efficient through increasing NO availability and NO synthase (5) can ultimately support elite athletes’ immense training and higher absolute workloads in exercise sessions.

We have observed the potential thermoregulatory mechanisms of NO in the athletes we train. Some athletes acutely report waiting to start exercise until their face has turned red and then note completing exponentially more aerobic work than without consuming NO. The flushing suggests NO may play a role in convective heat transfer from the blood to skin surface, controlling thermoregulatory heat generation, comparable with data regarding convective heat loss through skin increasing exercise time to exhaustion (1). Similarly, some tactical athletes love the feeling after NO consumption so extensively our dietitians limit the amount they consume on a daily basis. They comment on the ability to know when the supplement starts working and notice the increased capacity to complete more work. However, physiologically NO may cause diversion of blood to nonactive vascular beds or skin; therefore in overabundance it could compromise performance because of reduced oxygen delivery to active muscles.

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Bruce D. Johnson
Courtney M. Wheatley
Division of Cardiovascular Diseases
Mayo Clinic
Rochester, Minnesota
Amanda Carlson-Phillips
Laura J. Kunces
Nutrition and Research
EXOS
Phoenix, Arizona

CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?

TO THE EDITOR: In a recent Viewpoint, Jonvik et al. (4) discussed the role of dietary nitrate supplementation as an ergogenic aid for elite athletes. Although this author agrees with some statements of this article, I wish to raise some other key points on this issue. To date, there is little evidence supporting that increasing nitric oxide (NO) synthesis in athletes is a good approach to enhance exercise performance(1). On the other hand, it is worth mentioning that a chronic overproduction of NO has been associated with physiological dysfunctions, so I think it is important to raise a word of caution regarding the uncontrolled use of nitrate supplementation. Endogenous NO synthesis is tightly controlled in healthy subjects and exercise training has been found to increase NO availability, but this effect seems to dissipate if exercise is maintained due to physiological and anatomical adaptations (2). Importantly, and in accordance with this overview, baseline nitrate/nitrite levels in plasma of athletes do not seem to differ from those reported in healthy subjects (3). Although a recent study by Totzek et al. (5) found a significant correlation between plasma nitrite levels and the heart rate of lactate anaerobic threshold (LAT) in trained subjects, such findings have not been corroborated by others yet. Plasma is a well-known reservoir of nitrate/nitrite but we cannot discard that other parts of the body or cells can also act as an important storage of these anions in athletes and whether this fact is related with exercise capacity. Thus, this and other questions have to be addressed in future studies before recommending the use of moderate-high doses of dietary nitrate to elite athletes.

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Raul Bescos
School of Health Professions
University of Plymouth (United Kingdom)

WHO WINS AND/OR BENEFITS THE MOST?

TO THE EDITOR: Every athlete wants to be faster, jump higher, or be stronger than other competitors. Therefore, supplements with purported ergogenic benefits are widely used to enhance athletic performance. Indeed, several studies show that supplements effective at increasing nitric oxide (NO)- bioavailability (e.g., beetroot juice, sodium nitrate, and nitrite) improve performance in the recreational athlete. However, as Jonvik et al. (2) point out in this issue, the benefits may not always extend to elite athletes. Although the smallest but not scientifically measurable difference may be relevant, often there is no evidence that elite athletes benefit from dietary nitrate supplementation (1).

In economics, the “law of diminishing returns,” states that increasing input of a single component of a production process leads to progressively smaller increases in output. Applying this to elite athletes specializing in “performance” leads to the consideration that at some point further input of anything
contributing to that performance (e.g., NO) will yield diminishing returns.

However, there are humans that can greatly benefit from means to increase performance. Aging adults exhibit a downward trajectory of functional ability and supplementation could substantially alter rates of decline, thereby offsetting disability onset. NO bioavailability, which is markedly declined with advancing age, is essential for maintaining vascular endothelial function and is predictive of future cardiovascular disease (5). Studies show that increasing NO bioavailability via nitrate or nitrite supplementation improves functional cardiovascular and motor outcomes (3, 4). Therefore, nitrate and nitrite supplementation could provide greater benefits to older adults compared with elite athletes.

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COMMENT ON VIEWPOINT: CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?

TO THE EDITOR: Recent investigations have indicated that nutritional interventions aimed at increasing nitric oxide (NO) bioavailability (such as dietary nitrate or l-arginine supplementation) improve tolerance to exertion and time-trial performance, particularly in recreational athletes (1). The hypotheses proposed to explain these improvements in performance focused on the peripheral effects, such as the NO-mediated increase in muscular blood flow and efficiency of O_2 utilization. The possible dependence of these ergogenic effects on the NO bioavailability is not associated with NO-mediated central effects; in addition, possible differences in the susceptibility of recreational and elite athletes to the increased NO bioavailability cannot be explained by differences in the central nitrergic pathway.

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L. C. Johnson
C. R. Martens
J. N. Justice
S. B. Ballak
D. B. Ballak
1University of Colorado Boulder
2Dutch Olympic Committee*Dutch Sports Federation (NOC*NSF)
The Netherlands
3University of Colorado School of Medicine

COMMENT ON VIEWPOINT: CAN ELITE ATHLETES BENEFIT FROM DIETARY NITRATE SUPPLEMENTATION?

TO THE EDITOR: The Viewpoint article by Jonvik et al. (2) has raised an important and seemingly controversial issue on the reliability of dietary nitrate supplementation for enhancement of exercise performance in the elite athletes. Their proposed study design and methodological concerns (e.g., the need of a double-blinded, randomized multiple crossover n = 1 design) may provide some new insights in explaining some negative results obtained by different groups in highly trained cyclists and runners (1, 5). This individualized monitoring study design is likely to improve the sensitivity to detect potential benefits of dietary nitrate supplementation. In addition, one of the suggested mechanistic explanations is that the greater nitric oxide bioavailability in elite athletes blunts any benefits from additional nitrate supplementation (5). It is also possible that the different levels of other cellular signaling regulators such as hydrogen sulfate (H_2S) between untrained and elite athletes may also play a role. Indeed, a recent study reported enhanced tissue H_2S levels in beetroot juice-fed mice with a concomitant improvement in postischemic cardiac function (4). It may be worthwhile to quantify the circulating and skeletal muscle levels of nitrate and nitrite as well as H_2S among individual athletes to identify and differentiate those high responders vs. low responders to dietary nitrate supplementation. It would also be interesting to find out how NO and H_2S would work in
concert to modulate the skeletal muscle mitochondria function in response to dietary nitrate in the elite athletes, as previously shown in normal subjects (3).

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Shabina Rehman
Department of Physiology and Pharmacology
WVU School of Medicine